PATENT ABSTRACTS OF JAPAN

(11)Publication number : **10-130150**
(43)Date of publication of application : **19.05.1998**

(51)Int.Cl. A61K 31/505
C07D239/34
C07D239/42
C07D239/42

(21)Application number : **09-257573**
(22)Date of filing : **05.09.1997**

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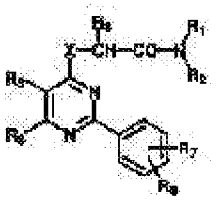
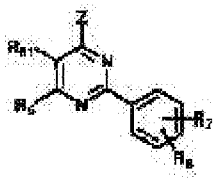
(30)Priority
Priority number : **08257704** Priority date : **05.09.1996** Priority country : **JP**

(54) **MEDICINE COMPRISING ACETIC ACID AMIDE DERIVATIVE**

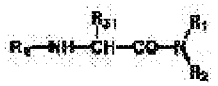


I

II



III



IV

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a medicine selectively and strongly acting on a peripheral benzodiazepine receptor, comprising a specific acetic acid amide derivative (acid addition salt) as an active ingredient.
SOLUTION: This medicine comprises an acetic acid amide derivative (acid addition salt) of formula I [X is O or NR4 (R4 is H, a lower alkyl, etc.); R1 is H, a lower alkenyl, etc.; R2 is a lower alkyl, a cycloalkyl, etc., or R1 and R2 together with adjoining N form a group of formula II (A is a single bond, NH, etc.; Ra and Rb are each H, a lower alkyl, etc.); R3 is H, a hydroxy (lower) alkyl, etc.; R5 is H, a lower alkenyl, etc.; R6 is H, trifluoromethyl, etc.; R7 is H, OH, etc.; R8 is H, halogen, etc.]. The compound of formula I is obtained by reacting a compound of formula III (Z is an eliminable atom or an eliminable group; R51 is R5 containing a protected amino, etc.) with a compound of formula IV (R31 is H, a lower alkyl, etc.) and optionally eliminating the protection group of the reaction product.

LEGAL STATUS

[Date of request for examination]

[Date of sending the examiner's decision of rejection]

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

[Number of appeal against examiner's decision of rejection]

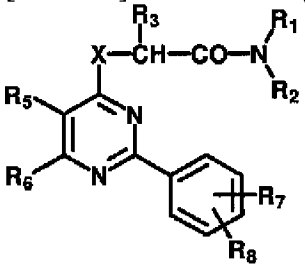
[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

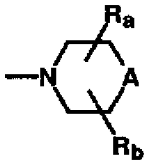
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] The following type [** 1]



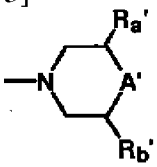
X means -O- or -NR4- among [type. R1 A hydrogen atom, A low-grade alkyl group and low-grade alkenyl radical or a cycloalkyl (low-grade) alkyl group is meant. R2 A low-grade alkyl group and cycloalkyl radical, unsubstituted, a permutation phenyl group, unsubstituted, or a permutation phenyl (low-grade) alkyl group is meant, or it is R1. And R2 The radical which becomes together with an adjoining nitrogen atom and is expressed with the following type is formed, and it is [Formula 2].



(Among a formula, A means single bond, -CH2-, -O-, or -NH-, and it differs, and a hydrogen atom or a low-grade alkyl group is meant, or A is single bond, that Ra and Rb are the same or when Ra and Rb are located in the 2nd place and the 3rd place, respectively, the carbon atom of the 2nd place and the 3rd place, Ra, and Rb may become together, and it may form a phenyl ring.)
R3 A hydrogen atom, a low-grade alkyl group, or a hydroxy (low-grade) alkyl group is meant. R4 A hydrogen atom or a low-grade alkyl group is meant, or it is R3. And R4 It becomes together with the carbon atom and nitrogen atom which they combine. Pyrrolidine, A piperidine or 2, and 3-dihydro-1H-Indore ring is formed, and it is R5. Hydrogen atom, A low-grade alkyl group and low-grade alkenyl radical, a hydroxy (low-grade) alkyl group, Unsubstituted or a permutation benzyloxy (low-grade) alkyl group, an acyloxy (low-grade) alkyl group, A low-grade alkoxy (low-grade) alkyl group, a trifluoromethyl radical, a halogen atom, The amino group, monochrome or a JI low-grade alkylamino radical, the acylamino radical, An amino (low-grade) alkyl group, a nitro group, a carbamoyl group, monochrome, or a JI low-grade alkyl carbamoyl group, A carboxyl group, the protected carboxyl group, a carboxy (low-grade) alkyl group, or the protected carboxy (low-grade) alkyl group is meant. R6 becomes together. A hydrogen atom, low-grade alkyl group, and trifluoromethyl radical, unsubstituted, or a permutation phenyl group is meant, or it is R5. And R6 - (CH2) It is n. - (in here) n -- 3, 4, 5, or 6 --

meaning -- forming -- R7 a hydrogen atom and a halogen atom -- a low-grade alkyl group, a lower alkoxy group, a trifluoromethyl radical, a hydroxy group, the amino group, monochrome or a JI low-grade alkylamino radical, a cyano group, or a nitro group -- meaning -- R8 A hydrogen atom, a halogen atom, a low-grade alkyl group, or a lower alkoxy group is meant.] Physic which comes out and consists of an acetic-amide derivative expressed or its acid addition salt permitted physiologically.

[Claim 2] R1 And R2 the same -- or -- or it differs and is a low-grade alkyl group -- R1 a low-grade alkyl group and low-grade alkenyl radical or a cycloalkyl (low-grade) alkyl group -- it is -- R2 or it is unsubstituted or a permutation phenyl group -- R1 [or] and the nitrogen atom with which R2 adjoins -- together -- becoming -- the following formula [** 3]

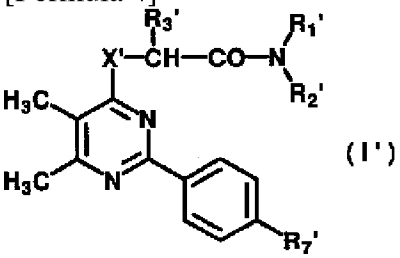


(-- A' means -CH2- or -O- among a formula, and Ra' and Rb' are the same -- or it differs and a low-grade alkyl group is meant.) -- physic which consists of a compound according to claim 1 which is the radical expressed.

[Claim 3] R1 And R2 the same -- or -- differing -- respectively -- a methyl group and an ethyl group -- It is a propyl group isopropyl group or butyl, or is R1. Methyl group, They are an ethyl group, a propyl group, an isopropyl group, butyl, an allyl group, or a cyclopropyl methyl radical. R2 It is the phenyl group permuted by the phenyl group, the halogen, or methoxy. R3 It is a hydrogen atom and is R5. They are a hydrogen atom, a methyl group, an ethyl group, or a hydroxymethyl group. R6 It is a methyl group or a phenyl group, or is R5. And R6 Become together and -(CH2) 4- is formed. R7 A hydrogen atom, a halogen atom, and C1 - C3 It is an alkoxy group, a trifluoromethyl radical, an amino group, or a nitro group, and is R8. Physic which consists of a compound according to claim 1 which is a hydrogen atom.

[Claim 4] The following type (I')

[Formula 4]



(I')

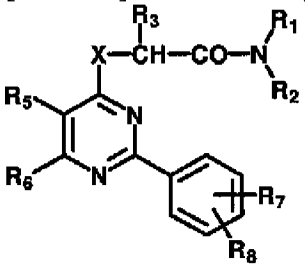
(Whether X' means -O- or -NR4"- among a formula, and both R1' and R2' mean an ethyl group or a propyl group) R1' or a methyl group, an ethyl group, a propyl group, an allyl group, or a cyclopropyl methyl radical R2' means a phenyl group, a 4-halogeno phenyl group, or 4-methoxypheny radical. R3' -- a hydrogen atom -- meaning -- R4' -- 'means a hydrogen atom, a methyl group, or an ethyl group, and R7' means a hydrogen atom, a halogen atom, a methoxy group, a trifluoromethyl radical, the amino group, or a nitro group. Physic which consists of an acetic-amide derivative expressed or its acid addition salt permitted physiologically.

[Claim 5] A 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N-methyl-N-phenyl acetamide, 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N and N-dipropyl acetamide, 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N and N-diethyl acetamide, An N-(4-chlorophenyl)-N-methyl-2-(5, 6-dimethyl-2-phenyl-4-pyrimidinyl amino) acetamide, A 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N-(4-fluoro phenyl)-N-methyl acetamide, A 2-(5, 6-dimethyl-2-phenyl-4-pyrimidinyl amino)-N-phenyl-N-propyl acetamide, A 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N-ethyl-N-phenyl acetamide, A 2-[methyl-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl] amino]-N-phenyl-N-propyl acetamide, And physic which consists of one which is chosen from 2-[5 and 6-dimethyl-2-(4-trifluoro methylphenyl)-4-pyrimidinyl amino]-N and N-dipropyl acetamide of a compound or its acid addition salt permitted physiologically.
[Claim 6] Physic which consists of a 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N-(4-methoxypheny)-N-methyl acetamide or its acid addition salt permitted physiologically.
[Claim 7] The uneasy associated-diseases remedy which makes an active principle a compound or its acid addition salt permitted physiologically given in any 1 term of claims 1-5.
[Claim 8] The uneasy associated-diseases remedy which makes an active principle a 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N-(4-methoxypheny)-N-methyl acetamide or its acid addition salt permitted physiologically.
[Claim 9] The immune inflammation disease remedy which makes an active principle a compound or its acid addition salt permitted physiologically given in any 1 term of claims 1-5.
[Claim 10] The immune inflammation disease remedy which makes an active principle 2-[5 and 6-dimethyl-2-(4-trifluoro methylphenyl)-4-pyrimidinyl amino]-N and N-dipropyl acetamide or its acid addition salt permitted physiologically.
[Claim 11] An N and N-dimethyl-2-[5 and 6-dimethyl-2-(4-trifluoro methylphenyl)-4-pyrimidinyl amino] acetamide, An N and N-diethyl-2-[5 and 6-dimethyl-2-(4-trifluoro methylphenyl)-4-pyrimidinyl amino] acetamide, And the immune inflammation disease remedy which makes an active principle one which is chosen from 2-[methyl-[5 and 6-dimethyl-2-(4-trifluoro methylphenyl)-4-pyrimidinyl] amino]-N and N-dipropyl acetamide of a compound or its acid addition salt permitted physiologically.

[Translation done.]

CLAIMS

[Claim(s)]
[Claim 1] The following type [** 1]



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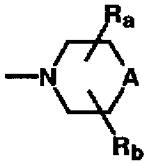

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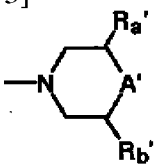

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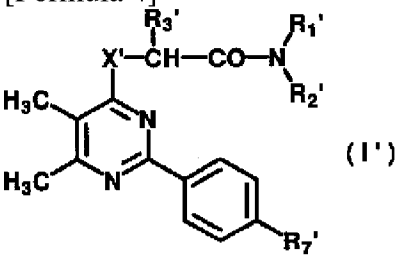
[Claim 4] The following type (I')

[Formula 4]



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[Claim 5] A 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N-methyl-N-phenyl acetamide, 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N and N-dipropyl acetamide, 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N and N-diethyl acetamide, An N-(4-chlorophenyl)-N-methyl-2-(5, 6-dimethyl-2-phenyl-4-pyrimidinyl amino) acetamide, A 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N-(4-fluoro phenyl)-N-methyl acetamide, A 2-(5, 6-dimethyl-2-phenyl-4-

pyrimidinyl amino)-N-phenyl-N-propyl acetamide, A 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N-ethyl-N-phenyl acetamide, A 2-[methyl-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl] amino]-N-phenyl-N-propyl acetamide, And physic which consists of one which is chosen from 2-[5 and 6-dimethyl-2-(4-trifluoro methylphenyl)-4-pyrimidinyl amino]-N and N-dipropyl acetamide of a compound or its acid addition salt permitted physiologically.

[Claim 6] Physic which consists of a 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N-(4-methoxypheny)-N-methyl acetamide or its acid addition salt permitted physiologically.

[Claim 7] The uneasy associated-diseases remedy which makes an active principle a compound or its acid addition salt permitted physiologically given in any 1 term of claims 1-5.

[Claim 8] The uneasy associated-diseases remedy which makes an active principle a 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N-(4-methoxypheny)-N-methyl acetamide or its acid addition salt permitted physiologically.

[Claim 9] The immune inflammation disease remedy which makes an active principle a compound or its acid addition salt permitted physiologically given in any 1 term of claims 1-5.

[Claim 10] The immune inflammation disease remedy which makes an active principle 2-[5 and 6-dimethyl-2-(4-trifluoro methylphenyl)-4-pyrimidinyl amino]-N and N-dipropyl acetamide or its acid addition salt permitted physiologically.

[Claim 11] An N and N-dimethyl-2-[5 and 6-dimethyl-2-(4-trifluoro methylphenyl)-4-pyrimidinyl amino] acetamide, An N and N-diethyl-2-[5 and 6-dimethyl-2-(4-trifluoro methylphenyl)-4-pyrimidinyl amino] acetamide, And the immune inflammation disease remedy which makes an active principle one which is chosen from 2-[methyl-[5 and 6-dimethyl-2-(4-trifluoro methylphenyl)-4-pyrimidinyl] amino]-N and N-dipropyl acetamide of a compound or its acid addition salt permitted physiologically.

[Translation done.]

TECHNICAL FIELD

[Field of the Invention] This invention relates to the physic which becomes a peripheral mold benzodiazepine acceptor from the new acetic-amide derivative which acts alternatively, and the acetic-amide derivative which has a 2-phenyl-4-pyrimidinyl amino part or a 2-phenyl-4-pyrimidinyl oxy-part in more detail.

[Translation done.]

PRIOR ART

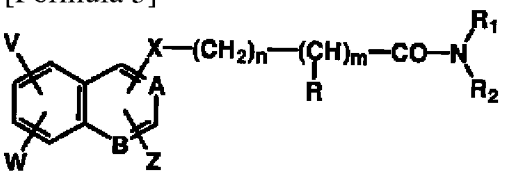
[Description of the Prior Art] There are three benzodiazepine (it may be hereafter written as "BZ") recognition sites in the central nervous system of the mammals including Homo sapiens, and it is called "the central mold (omega 1 and omega 2)" and the "peripheral mold (omega 3)" benzodiazepine acceptor, respectively ("BZomega1 acceptor", "BZomega2 acceptor", and "BZomega3 acceptor" may be called hereafter, respectively). Among these, since a peripheral mold BZ acceptor exists in the cell which shows maldistribution-distribution (the kidney, liver, heart, etc.) in a peripheral organization and a peripheral organ, and is especially concerned with living body inflammation immunomechanism, such as endocrine system organs, such as a suprarenal gland and a testis, a mast cell, a lymphocyte, a macrophage, and a platelet, deeply at high density, the interest about the physiological role is increasing recently. On the other hand, in the brain, it exists in the mitochondrial membrane of a neuroglia mostly, and participates in the incorporation by mitochondrial membrane Uchi of cholesterol, and it is thought that the biosynthetic path to AROPUREGUNANORON, AROTE truck hydronalium deoxycorticosterone (THDOC), etc. which are called a neuro-steroid through pregnenolone is affected. Therefore, if a peripheral mold BZ acceptor is stimulated, generation of the neuro-steroid within a brain will be promoted. Gamma-aminobutyric acid (hereafter) The joint device to a unique recognition site is neuro-minded [with which writing it as "gamma-aminobutyric acid" also exists in a certain a acceptor]. It is thought that Cl ion channel opening process is affected [Romeo, E. and others, J.Pharmacol.Exp.Ther., 262, and refer to 971-978 (1992)].

[0003] Since it was reported by JP,58-201756,A, the compound in which it has non-BZ frame and compatibility is alternatively shown to a peripheral mold BZ acceptor has been considerable-number-reported in patent application etc. However, there is no compound put in practical use as drugs.

[0004] It has non-BZ frame and the compound indicated by JP,62-5946,A and JP,2-32058,A other than the above is known as a compound in which alternative compatibility is shown to a peripheral mold BZ acceptor. The amides expressed with the following formula to JP,62-5946,A combine with peripheral mold BZ acceptors, and it is indicated to be useful as an immunodeficiency disease-like remedy by an anti-anxiety agent, antispasmodic and the antianginal agent, and the list.

[0005]

[Formula 5]



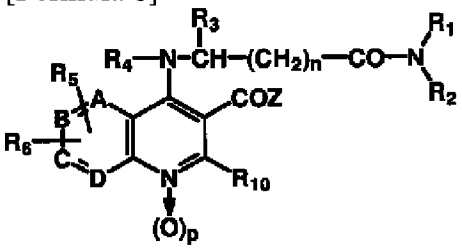
[0006] A shows a nitrogen atom or =CH- among [type, and B shows a nitrogen atom or =CH-. V and W A carbon number is the alkyl or alkoxy ** of 1-3, respectively. even if the same -- or -- differing -- **** -- hydrogen and a halogen -- Alt.**** is combined for Z by the para position about B. And phenyl, alkoxy ** or thienyl and pyridyl are shown -- or a halogen -- respectively -- a carbon number -- the alkyl of 1-4 -- and The phenyl permuted by one piece or two substituents which are chosen as a trifluoromethyl list from nitroglycerine is shown. Chain-X-(CH2) n-(CHR) m-CONR one R2 Alt.**** is combined by the para position about B. R -- hydrogen or a carbon number -- the alkyl of

1-3 -- being shown -- R1 And R2 You may differ, even if the same. A carbon number, respectively The alkyl of the shape of the line of 1-6, or a branched chain, A carbon number The cycloalkyl, the phenyl, phenyl alkyl whose carbon numbers of cycloalkyl the carbon numbers of an alkyl group are 1-3, respectively, and are 3-6, or cycloalkyl alkyl of 3-6, or the carbon number with which the double bond is not put on 1 and 2-location about the nitrogen atom -- three to 6 alkenyl -- being shown -- R1 And R2 It becomes together with the nitrogen atom which they have combined. A pyrrolidine, a piperidine, A morpholine or a thio morpholine ring can also be formed. X -CHR3-, - NR4-, -SO-, -SO2-, oxygen, or sulfur is shown, and it is R3. A hydrogen atom or a carbon number shows the alkyl of 1-3. R4 A carbon number shows the alkyl of 1-3, and m is 0 or 1, and n is 0, 1, or 2. As conditions When X shows -SO-, -SO2-, or -NR4- By the sum total of m+n being equal to at least 1, and A and B showing a nitrogen atom, respectively, when Z is in a para position about B X is not -CHR3-, and A shows =CH-, B shows nitrogen, Z is in an alt.location about B, and X shows oxygen, and when R shows hydrogen the sum total of m+n is except one and, moreover, excepts 2-phenyl-4-quinolyl-N and N-dimethyl carbamate.]

[0007] In JP,2-32058,A, the 4-amino-3-carboxy quinolines expressed with the following formula have compatibility to a peripheral mold BZ acceptor by in vitro one and in vivo one, and it is indicated to be able to use it for prevention or the therapy of the shape of an infectious disease as prevention and the therapy of a human cardiovascular disorder, or an antiallergic drug, or the therapy of an uneasy symptom.

[0008]

[Formula 6]



[0009] R1 and R2 among [type, respectively Hydrogen, the alkyl of C1-C6, or C2-C6 or it is chosen out of the alkenyl, phenyl, or benzyl -- R1 and R2 [or] In the nitrogen atom which they have combined, it is C4-C8. It forms saturation heterocyclic. R3 Hydrogen and C1-C6 Alkyl, phenyl, or C7-C9 It is chosen out of phenyl alkyl. R4 Hydrogen or C1-C4 it chooses out of alkyl -- having -- R5 And R6 Respectively, they are hydrogen or a halogen, and C1-C3. Alkyl or alkoxy ** It is chosen out of nitroglycerine or trifluoromethyl, or is united, and a methylene dioxy radical is formed. Z is OR7. It is [it is chosen out of alkyl of hydrogen or C1-C6 by inside R7 of formula];NR eight R9. Inside of [type, R8 And R9 respectively -- hydrogen and C1-C4];C1-C4 chosen from alkyl, phenyl, or benzyl alkyl; -- benzyl; -- C4-C6 which does not have or have a different term atom It is aryl. R10 is the alkyl or phenyl (however, R3 is not H when Z is not the benzyl or the aryl.) of hydrogen and C1-C4. a phenyl group and benzyl -- a halogen and C1-C3 it permutes by alkoxy ** alkyl or thio alkyl, nitroglycerine, trifluoromethyl, or HIDOROKISHI -- having -- **** -- here -- alkyl and alkoxy ******, and branching -- it is annular. n of 0, 1, or 2p is [0 or 1, and 1 of Notations A, B, C, and D] N, and, as for others, CH, or A, B, C and D express CH, respectively.]

[0010] On the other hand, some acetic-amide derivatives which have a 2-phenyl-4-pyrimidinyl amino part are known. for example, on U.S. Pat. No. 3631036 specifications The compound represented by 2-(5-cyano-2-phenyl-4-pyrimidinyl amino) acetamide as synthetic intermediate field of the 5-amino -2 and the 6-JI permutation-7H-[2 and 3-pyrrolo d] pyrimidines moreover The compound represented by 2-(5-cyano - 6-methylamino-2-phenyl-4-pyrimidinyl amino) acetamide is only indicated by the U.S. Pat. No. 3631045 specification as synthetic intermediate field of the 4 and 5-diamino-7H-[2 and 3-pyrrolo d] pyrimidines. The pharmacological action of those compounds is not reported at all.

[0011] moreover, to Pharmazie, 43, and 537-538 (1988) 2- To a (5-acetyl-6-methyl-2-phenyl-4-pyrimidinyl thio)-N-(4-chlorophenyl) acetamide and a 2-(5-acetyl - 6-methyl-2-phenyl-4-pyrimidinyl thio)-N-(4-methylphenyl) acetamide Some compounds represented are indicated as synthetic intermediate field of the [2 and 3-thieno d] pyrimidine derivative. Furthermore, it is indicated that a 2-(5-acetyl - 6-methyl-2-phenyl-4-pyrimidinyl thio)-N-(4-chlorophenyl) acetamide shows an antibacterial action to Bacillus subtilis.

[Translation done.]

EFFECT OF THE INVENTION

[Effect of the Invention] As explained above, the compound expressed with a formula (I), and its acid addition salt permitted physiologically Peripheral mold BZomega3 While alternative and remarkable compatibility is shown to an acceptor Since an animal trial also shows the outstanding pharmacological actions, such as an antianxiety effect and an anti-epilepsy operation, it is useful as the remedy and prophylactics of a circulatory system disease, such as central diseases, such as uneasy associated diseases (neurosis, a psychosomatic disease, other anxiety disorder), depression, and epilepsy, angina pectoris, and hypertension. Moreover, the compound expressed with a formula (I) and its acid addition salt permitted physiologically are expected as the remedy and prophylactics of an immune inflammation disease, such as immune nervous diseases, such as multiple sclerosis, or rheumatism.

TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] this invention persons are BZomega3. As a result of repeating research wholeheartedly in order to obtain the physic which becomes an acceptor from the compound which acts alternatively and powerfully, a header and this invention were completed for the physic which consists of an acetic-amide derivative expressed with the after-mentioned type (I) agreeing for this purpose.

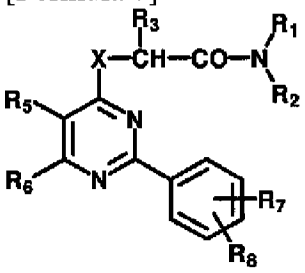
[Translation done.]

MEANS

[Means for Solving the Problem] According to this invention, the physic which consists of an acetic-amide derivative expressed with the following formula (I) and its acid addition salt ("the compound concerning this invention" may be called hereafter) permitted physiologically is offered.

[0014]

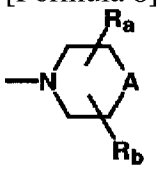
[Formula 7]



(I)

[0015] X means -O- or -NR4- among [type. R1 A hydrogen atom, A low-grade alkyl group and low-grade alkenyl radical or a cycloalkyl (low-grade) alkyl group is meant. R2 A low-grade alkyl group and cycloalkyl radical, unsubstituted, a permutation phenyl group, unsubstituted, or a permutation phenyl (low-grade) alkyl group is meant, or it is R1. And R2 The radical which becomes together with an adjoining nitrogen atom and is expressed with the following type is formed, and it is [0016].

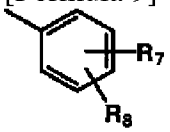
[Formula 8]



[0017] Or it differs, and a hydrogen atom or a low-grade alkyl group is meant, or A is single bond. A means single bond, -CH2-, -O-, or -NH- among a formula, and Ra and Rb are the same -- Ra And Rb the time of being located in the 2nd place and the 3rd place, respectively -- the carbon atom of the 2nd place and the 3rd place, and Ra And Rb It may become together and a phenyl ring may be formed. R3 A hydrogen atom, a low-grade alkyl group, or a hydroxy (low-grade) alkyl group is meant. R4 A hydrogen atom or a low-grade alkyl group is meant, or it is R3. And R4 It becomes together with the carbon atom and nitrogen atom which they combine. Pyrrolidine, A piperidine or 2, and 3-dihydro-1H-Indore ring is formed, and it is R5. Hydrogen atom, A low-grade alkyl group and low-grade alkenyl radical, a hydroxy (low-grade) alkyl group, Unsubstituted or a permutation benzyloxy (low-grade) alkyl group, an acyloxy (low-grade) alkyl group, A low-grade alkoxy (low-grade) alkyl group, a trifluoromethyl radical, a halogen atom, The amino group, monochrome or a JI low-grade alkylamino radical, the acylamino radical, An amino (low-grade) alkyl group, a nitro group, a carbamoyl group, monochrome, or a

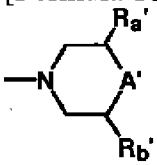
JI low-grade alkyl carbamoyl group, A carboxyl group, the protected carboxyl group, a carboxy (low-grade) alkyl group, or the protected carboxy (low-grade) alkyl group is meant. R6 becomes together. A hydrogen atom, low-grade alkyl group, and trifluoromethyl radical, unsubstituted, or a permutation phenyl group is meant, or it is R5. And R6 - (CH2) It is n. - (in here) n -- 3, 4, 5, or 6 -- meaning -- forming -- R7 a hydrogen atom and a halogen atom -- a low-grade alkyl group, a lower alkoxy group, a trifluoromethyl radical, a hydroxy group, the amino group, monochrome or a JI low-grade alkylamino radical, a cyano group, or a nitro group -- meaning -- R8 A hydrogen atom, a halogen atom, a low-grade alkyl group, or a lower alkoxy group is meant.]
[0018] With the acid addition salt of the compound expressed with a formula (I) permitted physiologically The acid addition salt of the compound of the formula in the case of having sufficient basicity being able to form an acid addition salt (I) permitted physiologically is meant. For example, organic-acid salts, such as inorganic-acid salts, such as a hydrochloride, hydrobromate, a hydroiodic-acid salt, a sulfate, and phosphate, and a maleate, a fumaric-acid salt, an oxalate, citrate, a tartrate, a lactate, a benzoate, and a methansulfonic acid salt, are mentioned. Since the compound expressed with a formula (I) and its acid addition salt may exist in the form of a hydrate and/or solvate, such hydrates and solvates are also included by the compound concerning this invention.
[0019] The compound of a formula (I) has one or more asymmetric carbon atoms by the case, and may produce geometrical isomerism. Therefore, the compound of a formula (I) may exist in the form of two or more sorts of stereoisomers by the case. These stereoisomers, the mixture of those, and racemic modification are included by the compound concerning this invention.
[0020] The vocabulary in this specification is explained below.
[0021] A low-grade alkyl group and especially a low-grade alkyl part may mean the thing of the carbon atomic numbers 1-6, unless it refuses, and any of the shape of the shape of a straight chain and a branched chain are sufficient as them. As an example of a "low-grade alkyl group", methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, and hexyl are mentioned. R3, R4, R5, R6, and R7 And as a low-grade alkyl group of R8, the thing of the carbon atomic numbers 1-4 is desirable. Methoxy and ethoxy ** propoxy and butoxy one are mentioned as an example of a "lower alkoxy group." A "low-grade alkenyl radical" means the thing of the carbon atomic numbers 3-6 which have [except in between] the one to 2nd place of one double bond, for example, an allyl compound and 2-butenyl are mentioned. A "cycloalkyl radical" means the thing of the carbon atomic numbers 3-8, and cyclo propyl, cyclo butyl, cyclopentyl, cyclohexyl, cycloheptyl one, and cyclo octyl are mentioned as an example. A "cycloalkyl (low-grade) alkyl group" means the alkyl group of the carbon atomic numbers 1-4 which the above "a cycloalkyl radical" has permuted, for example, cyclopropyl methyl, cyclopentyl methyl, and cyclohexyl methyl are mentioned. A "halogen atom" means a fluorine, chlorine, a bromine, and iodine.
[0022] They are a halogen atom, and C1 - C3 as "unsubstituted or a permutation phenyl group". Alkyl, C1 - C3 Alkoxy ** trifluoromethyl, amino, monochrome, or JI (C1-C3) alkylamino, The phenyl group which may be permuted by one piece chosen from cyano **** nitroglycerine or two pieces is meant. For example, phenyl; 2-, 3- Or 4-chlorophenyl; 2-, 3- Or 4-BUROMO phenyl; 2-, 3- Or 4-fluoro phenyl; 2, 4-dichlorophenyl;2, 4-dibromo phenyl;2, and 4-difluoro phenyl;2-, 3- or 4-methylphenyl;2-,

3- or 4-methoxypheny;2-, 3- or 4-trifluoro methylphenyl;2-, 3- Or 4-aminophenyl; 2-, 3- or 4-methylamino phenyl;2-, 3- or 4-dimethylaminophenyl;2-, 3- or 4-cyanophenyl;2-, 3-, or 4-nitrophenyl is mentioned.
[0023]
[Formula 9]



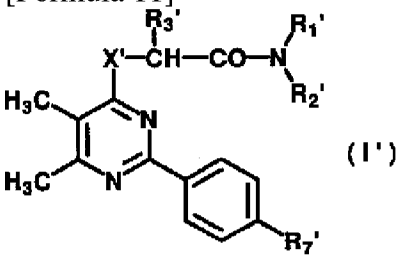
[0024] Although what was enumerated in the part of the above "unsubstituted or a permutation phenyl group" can be mentioned as it is as an example of a radical expressed with the above-mentioned formula, as a suitable example, phenyl, 4- or 3-chlorophenyl, 4- or 3-BUROMO phenyl, 4- or 3-fluoro phenyl, and 4-methoxypheny can be mentioned. "Unsubstituted or a permutation phenyl (low-grade) alkyl group" means the alkyl group of the carbon atomic numbers 1-4 permuted by the above-mentioned "unsubstituted [above-mentioned] or permutation phenyl group", for example, benzyl;2-, 3-, 4-chloro benzyl;4-BUROMO benzyl;3-, or 4-fluoro benzyl;4-methylbenzyl;4-methoxybenzyl; phenethyl;2-(4-chlorophenyl) ethyl is mentioned.
[0025] A "hydroxy (low-grade) alkyl group" means the alkyl group of the carbon atomic numbers 1-4 permuted by the hydroxy group, for example, hydroxymethyl, 2-hydroxyethyl, and 3-hydroxypropyl are mentioned. With "unsubstituted or a permutation benzyloxy (low-grade) alkyl group" A halogen, and C1 - C3 The hydroxy (low-grade) alkyl group permuted by the benzyl by which the phenyl part may be permuted by one piece chosen from C1 - alkyl and C3 ARUKOKISHI or two pieces is meant. For example, benzyloxymethyl; 2-, 3- Or 4-chloro benzyloxymethyl; 3-BUROMO benzyloxymethyl; -- 4-fluoro benzyloxymethyl; -- 2 and 4- or 3, 4-dichloro benzyloxymethyl;4-methylbenzyl oxymethyl;2-, 3-, or 4-methoxybenzyl oxymethyl;2-benzyloxy ethyl is mentioned. They are the alkanoyl radical of the carbon atomic numbers 2-4 or a halogen, and C1 - C3 as an "acyl group". Alkyl, or C1 - C3 The benzoyl which may be permuted by ARUKOKISHI is meant, for example, acetyl; propionyl; benzoyl;2-, 3- or 4-chloro benzoyl;2-, 3- or 4-BUROMO benzoyl;2-, 3-, or 4-fluoro benzoyl;4-methylbenzoyl;4-methoxy benzoyl is mentioned. An "acyloxy (low-grade) alkyl group" means the hydroxy (low-grade) alkyl group permuted above "an acyl group", for example, acetoxy methyl; benzoyl oxymethyl;4-chlorobenzo yloxy methyl;3-bromobenzoyloxy methyl;4-fluoro benzoyl oxymethyl;2-methylbenzoyl oxymethyl;4-methoxy benzoyl oxymethyl is mentioned. A "low-grade alkoxy (low-grade) alkyl group" means the alkyl group of the carbon atoms 1-4 permuted by ARUKOKISHI of the carbon atomic numbers 1-4, for example, methoxymethyl, ethoxymethyl, 2-methoxy ethyl, and 3-methoxy propyl are mentioned.
[0026] As for "monochrome or a JI low-grade alkylamino radical", the alkyl group of the carbon atomic numbers 1-4 means one piece or the amino group permuted two pieces, for example, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, and ethyl methylamino are mentioned. The "acylamino radical" means the amino group permuted by the above-mentioned "acyl group", for example, acetylamino, propionylamino, benzoylamino, 4-chlorobenzo ylamino, and 4-fluorobenzo ylamino are mentioned. An "amino (low-grade) alkyl group" means the alkyl group of the

carbon atomic numbers 1-4 permuted by the amino group, for example, aminomethyl, 2-aminoethyl, and 3-aminopropyl are mentioned. "Monochrome or a JI low-grade alkyl carbamoyl group" means the carbamoyl group permuted by one alkyl group of the carbon atomic numbers 1-4, or two pieces, for example, methylcarbamoyl, dimethyl carbamoyl, diethylcarbamoyl, and dipropyl carbamoyl are mentioned. The protective group from which it may be desorbed by hydrolysis or hydrogenolysis with "the protected carboxyl group", For example, C1-C4 An alkyl group or a halogen, and C1 - C3 Alkyl, and C1 - C3 The carboxyl group protected by the benzyl which may be permuted by one piece chosen from ARUKOKISHI or two pieces is meant. As an example, methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl, Although butoxycarbonyl, benzyloxycarbonyl, 4-chloro benzyloxycarbonyl, 4-fluoro benzyloxycarbonyl, 4-methylbenzyl oxycarbonyl, and 4-methoxybenzyl oxycarbonyl are mentioned Methoxycarbonyl, ethoxycarbonyl, and benzyloxycarbonyl are desirable. The alkyl group of the carbon atomic numbers 1-4 permuted by "the carboxyl group described above " protected with protected carboxy (low-grade) alkyl group"" is meant, for example, methoxy carbonylmethyl, ethoxy carbonylmethyl, benzyloxy carbonylmethyl, and 2-ethoxy carbonylethyl are mentioned.
[0027] a thing suitable among the compounds concerning this invention -- a formula (I) -- setting -- R1 and R2 is the same -- or -- or it differs and is a low-grade alkyl group, respectively -- R1 a low-grade alkyl group and low-grade alkenyl radical or a cycloalkyl (low-grade) alkyl group -- it is -- R2 or it is unsubstituted or a permutation phenyl group -- R1 [or] And R2 [the radical which becomes together with an adjoining nitrogen atom and is expressed with the following type -- forming -- 0028]
[Formula 10]



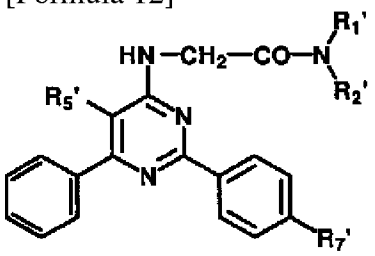
[0029] (A' means -CH2- or -O- among a formula, and Ra' and Rb' are the same -- or it differs and a low-grade alkyl group is meant.)
[0030] R5 It is a hydrogen atom, low-grade alkyl group, and hydroxy (low-grade) alkyl group, a halogen atom, the amino group, the acylamino radical, a nitro group, or the protected carboxy group, and is X, R3, R6, and R7. And R8 They are the compound which is the same as the above-shown, and its acid addition salt permitted physiologically.
[0031] The still more suitable thing among the compounds concerning this invention a formula (I) -- setting -- R1 And R2 the same -- or -- differing -- respectively -- a methyl group -- It is an ethyl group, a propyl group, an isopropyl group, or butyl, or is R1. Methyl group, They are an ethyl group, a propyl group, an isopropyl group, butyl, an allyl group, or a cyclopropyl methyl radical. R2 It is the phenyl group permuted by the phenyl group, the halogen, or methoxy. R3 is a hydrogen atom and it is R5. They are a hydrogen atom, a methyl group, an ethyl group, or a hydroxymethyl group. R6 It is a methyl group or a phenyl group, or is R5. And R6 Become together and -(CH2) 4- is formed. R7 A hydrogen atom, a halogen atom, and C1 - C3 It is an alkoxy group, a trifluoromethyl radical, an amino group, or a nitro group, R8 is a hydrogen atom, and it is X and R4. They are the compound which is the same as the above-shown, and its acid addition salt

permitted physiologically.
[0032] In a formula (I), X of a much more suitable compound is -O- or -NR4'-. R1 And R2 the same -- or -- or it differs and is an ethyl group, a propyl group, or butyl -- R1 [or] By a methyl group, the ethyl group, the propyl group, the allyl group, or the cyclopropyl methyl radical R2 It is a phenyl group, a halogeno phenyl group, or a methoxypheny radical, and is R3. By the hydrogen atom R4' is a hydrogen atom, a methyl group, or an ethyl group, or R3 and R4' become together with the carbon atom and nitrogen atom which they combine, and form a pyrrolidine or 2, and 3-dihydro-1H-Indore ring. R7 It is a hydrogen atom, a halogen atom, a methoxy group, a trifluoromethyl radical, an amino group, or a nitro group, and is R8. It is a hydrogen atom and is R5. And R6 They are the same compound as what was described immediately before, and its acid addition salt permitted physiologically.
[0033] As a suitable compound, the following type (I') or (I") the acetic-amide derivative expressed, and its acid addition salt permitted physiologically are mentioned especially.
[0034]
[Formula 11]



(I')

[0035] (Whether X' means -O- or -NR4"- among a formula, and both R1' and R2' mean an ethyl group or a propyl group) R1' or a methyl group, an ethyl group, a propyl group, an allyl group, or a cyclopropyl methyl radical R2' means a phenyl group, a 4-halogeno phenyl group, or 4-methoxypheny radical. R3' -- a hydrogen atom -- meaning -- R4' -- 'means a hydrogen atom, a methyl group, or an ethyl group, and R7' means a hydrogen atom, a halogen atom, a methoxy group, a trifluoromethyl radical, the amino group, or a nitro group.
[0036]
[Formula 12]



(I")

[0037] (a formula -- inside -- R -- five -- ' -- a hydrogen atom -- a methyl group -- or -- an ethyl group -- meaning -- R -- one -- ' -- R -- two -- ' -- R -- seven -- ' -- the above-shown -- being the same -- a thing -- meaning .)
[0038] As an example of a suitable compound, a following compound and its following acid addition salt permitted physiologically are mentioned especially, for example.
[0039] 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N and N-dipropyl

acetamide, [0040] 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N and N-diethyl acetamide, [0041] A 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N-methyl-N-phenyl acetamide, [0042] An N-(4-chlorophenyl)-N-methyl-2-(5, 6-dimethyl-2-phenyl-4-pyrimidinyl amino) acetamide, [0043] A 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N-(4-fluoro phenyl)-N-methyl acetamide, [0044] A 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N-(4-methoxypheny)-N-methyl acetamide, [0045] A 2-(5, 6-dimethyl-2-phenyl-4-pyrimidinyl amino)-N-phenyl-N-propyl acetamide, [0046] A 2-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl amino]-N-ethyl-N-phenyl acetamide, [0047] 2-(5, 6-dimethyl-2-phenyl-4-pyrimidinyl oxy-)-N and N-dipropyl acetamide, [0048] 2-(2, 6-diphenyl-4-pyrimidinyl amino)-N and N-dipropyl acetamide, [0049] 2-[5 and 6-dimethyl-2-(4-trifluoro methylphenyl)-4-pyrimidinyl amino]-N and N-dipropyl acetamide, [0050] A 2-[2-(4-aminophenyl)-5 and 6-dimethyl-4-pyrimidinyl oxy-]-N-ethyl-N-phenyl acetamide, [0051] An N-(4-chlorophenyl)-N-methyl-2-(5, 6-dimethyl-2-phenyl-4-pyrimidinyl oxy-) acetamide, [0052] A 2-(5, 6-dimethyl-2-phenyl-4-pyrimidinyl oxy-)-N-phenyl-N-propyl acetamide and [0053] 2-[methyl-[2-(4-chlorophenyl)-5 and 6-dimethyl-4-pyrimidinyl] amino]-N-phenyl-N-propyl acetamide.

[0054] The compound which is expressed as an example of the compound contained in the compound of a formula (I) in the following tables 1-6 in addition to the compound of the after-mentioned example, and its acid addition salt permitted physiologically are mentioned.

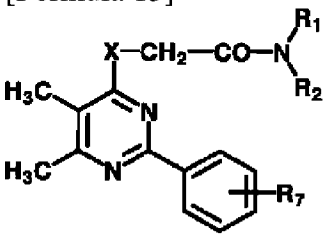
[0055] In addition, in the example of the after-mentioned reference, and an example, the following cable addresses may be used for Table 1 of this specification - 6 lists for simplification of a publication.

[0056] Ac : an acetyl group, Me : A methyl group, Et : An ethyl group, Pr : A propyl group, i-Pr : An isopropyl group, Bu : Butyl, i-Bu : An isobutyl radical, CH2**: A cyclopropyl methyl radical, Ph : Phenyl group.

[0057] Therefore, Ph-4-Cl 4-chlorophenyl radical and Ph-4-F express 4-fluoro phenyl group.

[0058]

[Formula 13]

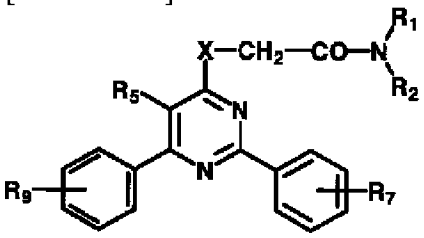


[0059]

[Table 1]

R_1	R_2	R_7	X	R_1	R_2	R_7	X
Me	Ph-2-F	H	NH	Bu	Bu	4-OMe	NH
Me	Ph-2-Br	H	NH	Me	Ph-3-F	4-OMe	NH
				Et	Ph-4-F	4-OMe	NH
i-Pr	i-Pr	4-Cl	NH	Pr	Pr	4-OH	NH
Me	Ph-2-Cl	4-Cl	NH	Me	Ph	4-NH_2	NH
Me	Ph-3-F	4-Cl	NH				
Et	Ph-4-Cl	4-Cl	NH	Bu	Bu	H	NMe
Et	Ph-4-F	4-Cl	NH	Me	Ph-4-Cl	4-F	NMe
				Me	Ph-4-F	4-Cl	NMe
Pr	Pr	2-Br	NH				
Pr	Pr	4-Br	NH	Pr	Pr	H	NEt
Bu	Bu	4-Br	NH	Pr	Pr	4-F	NEt
Me	Ph	4-Br	NH	Me	Ph	4-Cl	NPr
Me	Ph	4-Br	NH				
Et	Ph-4-Cl	4-Br	NH	Pr	Pr	4-NH_2	O
				i-Pr	i-Pr	4-Cl	O
Pr	Pr	3-F	NH	Bu	Bu	4-Cl	O
Me	Ph	2-F	NH				
Me	Ph-2-Cl	4-F	NH	Me	Ph	4-NH_2	O
Me	Ph-3-Cl	4-F	NH	Me	Ph-4-Cl	3-F	O
Me	Ph-2-F	4-F	NH	Me	Ph-2-F	4-Cl	O
Et	Ph-4-F	4-F	NH	Et	Ph-4-Cl	H	O
				Et	Ph-4-Cl	4-F	O
				Et	Ph-4-F	4-Cl	O

[0060]
[Formula 14]



[0061]
[Table 2]

R_1	R_2	R_5	R_9	R_7	X
Et	Et	H	H	4-Cl	NH
Pr	Pr	H	H	4-F	NH
Pr	Pr	H	H	2-F	NH
i-Pr	i-Pr	H	H	H	NH
Bu	Bu	H	H	H	NH
Bu	Bu	H	H	4-F	NH
Me	Ph	H	H	4-F	NH
Me	Ph	H	H	3-Cl	NH
Me	Ph-4-Cl	H	H	4-Cl	NH
Me	Ph-2-Cl	H	H	4-F	NH
Me	Ph-4-F	H	H	4-Cl	NH
Me	Ph-2-F	H	H	4-F	NH
Et	Ph	H	H	4-Cl	NH
Et	Ph-4-Cl	H	H	H	NH

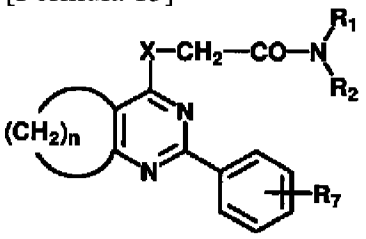
[0062]
[Table 3]
表２の続き

R_1	R_2	R_5	R_9	R_7	X
Pr	Pr	Me	H	4-F	NH
i-Pr	i-Pr	Me	H	4-Cl	NH
Bu	Bu	Me	H	4-F	NH
Me	Ph	Me	H	4-Cl	NH
Me	Ph-4-Cl	Me	H	H	NH
Me	Ph-4-Cl	Me	H	4-F	NH
Me	Ph-4-F	Me	H	4-Cl	NH
Et	Ph	Me	H	H	NH
Et	Ph	Me	H	4-Cl	NH
Pr	Pr	H	4-Cl	4-F	NH
Bu	Bu	H	4-NO_2	4-F	NH
Me	Ph-4-Cl	H	2-Me	H	NH
Pr	Pr	Me	4-Cl	4-F	NH
Bu	Bu	Me	4-NO_2	4-F	NH
Me	Ph-4-Cl	Me	2-Me	H	NH

[0063]
[Table 4]
表２の続き

R_1	R_2	R_5	R_9	R_7	X
Et	Et	H	H	3-Cl	O
Pr	Pr	H	H	4-Cl	O
i-Pr	i-Pr	H	H	4-F	O
Bu	Bu	H	H	4-Cl	O
Me	Ph	H	H	4-Cl	O
Me	Ph-4-Cl	H	H	4-F	O
Et	Ph	H	H	2-Cl	O
Et	Ph-4-Cl	H	H	H	O
Et	Et	Me	H	4-Cl	O
Pr	Pr	Me	H	H	O
Pr	Pr	Me	H	4-Cl	O
i-Pr	i-Pr	Me	H	3-F	O
Bu	Bu	Me	H	2-Cl	O
Me	Ph-4-Cl	Me	H	4-F	O
Et	Ph	Me	H	4-Cl	O
Et	Ph-4-Cl	Me	H	H	O
Pr	Pr	H	4-Cl	H	O
Me	Ph-4-Cl	H	4-NO_2	4-F	O
Pr	Pr	Me	4-F	4-Cl	O
Me	Ph	Me	4-OMe	4-F	O

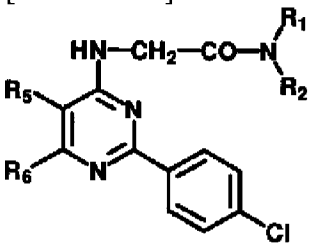
[0064]
[Formula 15]



[0065]
[Table 5]

R_1	R_2	n	R_7	X
Pr	Pr	3	4-Cl	NH
Pr	Pr	5	2-F	NH
Pr	Pr	3	4-F	O
Pr	Pr	5	H	O
Me	Ph	3	H	NH
Me	Ph	5	4-F	NH
Me	Ph-4-Cl	6	4-Cl	NH
Me	Ph-4-Cl	3	4-F	O
Me	Ph-4-F	5	H	O
Me	Ph-4-F	6	4-Cl	O

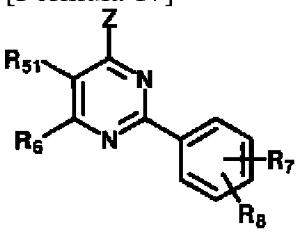
[0066]
[Formula 16]



[0067]
[Table 6]

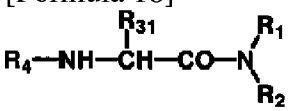
R_1	R_2	R_5	R_6	R_1	R_2	R_5	R_6
Me	Ph	$-CH_2CH_2OH$	H	Pr	Pr	Pr	Me
Pr	Pr	$-CH_2OCH_2Ph$	H	Pr	Pr	$-CH_2OH$	Me
Pr	Pr	$-CH_2OAc$	H	Pr	Pr	$-CH_2CH=CH_2$	Me
Pr	Pr	$-CH_2OCOPh$	H	Me	Ph	Me	Et
Me	Ph	$-CH_2OMe$	H	Me	Ph	Et	Et
Me	Ph	-NHMe	H	Me	Ph	Pr	Pr
Me	Ph	$-NEt_2$	H	Me	Ph	Me	CF_3
Me	Ph	$-CH_2NH_2$	H				
Me	Ph	$-CONH_2$	H	Me	Ph	-COOEt	H
Pr	Pr	-CONHMe	H	Me	Ph	$-COOCH_2Ph$	H
Pr	Pr	$-CONEt_2$	H	Pr	Pr	$-CH_2COOH$	H
Me	Ph	-COOH	H	Pr	Pr	$-CH_2COOEt$	H

[0068] The compound of a formula (I) can be manufactured by the following approaches.
[0069] The compound whose X is -NR4- in a process (a) type (I) is the following formula (II).
[0070]
[Formula 17]



(II)

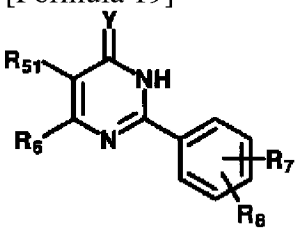
[0071] Z means a desorption atom or a leaving group among [type, the same thing as what the above-shown R5 defined except for R51 replacing the form where a hydroxy (low-grade) alkyl group, the amino group, the amino (low-grade) alkyl group, the carboxyl group, and the carboxy (low-grade) alkyl group were protected is meant, and R6, R7, and R8 mean the same thing as the above-shown.] The compound and the following type [0072] which are come out of and expressed (III)
[Formula 18]



(III)

[0073] Among [type, R31 means a hydrogen atom, a low-grade alkyl group, or the protected hydroxy (low-grade) alkyl group, and R1, R2, and R4 mean the same thing as the above-shown.] It can come out, the compound expressed can be made to be able to react, and it can manufacture by desorbing the protective group of a product if needed.
[0074] The desorption atom or leaving group expressed with Z in a formula (II) means the atom or radical from which it may be desorbed in the form of HZ with the hydrogen atom of NH part of the compound of a formula (III) under a reaction condition, for example, an arylsulfonyloxy radical like a halogen atom like chlorine, a bromine, and iodine, a low-grade alkylsulfonyloxy radical like methane sulfonyloxy, a trihalogeno methane sulfonyloxy radical like trifluoromethane sulfonyloxy, benzene sulfonyloxy, and p-toluenesulfonyloxy is mentioned.
[0075] The protected hydroxy group which is shown by R31 and R51 of the above-mentioned formula (II) and a formula (III) means the hydroxy group protected by the protective group from which it may be desorbed by hydrogenolysis, for example, benzyloxy one, 4-chloro benzyloxy, 3-BUROMO benzyloxy, 4-fluoro benzyloxy, 4-methyl benzyloxy, and 4-methoxybenzyloxy are mentioned. The protected amino group or amino part which is shown by R51 in a formula (II) means the amino group or amino part protected by the protective group from which it may be desorbed by hydrogenolysis, for example, benzyloxycarbonylamino, 3- or 4-chloro benzyloxycarbonylamino, 4-BUROMO benzyloxycarbonylamino, 4-fluoro benzyloxycarbonylamino, 4-methylbenzyl oxy carbonyl amino, and 4-methoxybenzyloxy carbonylamino are mentioned. The protected carboxyl group or carboxy part which is shown by R51 in a formula (II) means the carboxyl group or carboxy part protected by the protective group from which it may be desorbed by hydrolysis or hydrogenolysis, and what was explained in full detail in the

explanation part of said vocabulary as an example is mentioned.
[0076] The compound and formula (III) which are expressed with a formula (II) The reaction with the compound expressed is performed under un-existing [of a solvent], or in a suitable solvent to the bottom of ordinary pressure or pressurization.
[0077] Alcohols like the ketones like toluene, the aromatic hydrocarbon like a xylene, a methyl ethyl ketone, and methyl isobutyl ketone as an example of a solvent, dioxane, ether like a jig lime, ethanol, isopropanol, and a butanol, an acetonitrile, dimethylformamide, and dimethyl sulfoxide are mentioned. It is a formula (III), although it is desirable to perform this reaction to the bottom of existence of a base and carbonic acid hydrogen alkali like carbonic acid alkali like a sodium carbonate and potassium carbonate as an example of a base, a sodium hydrogencarbonate, and a potassium hydrogencarbonate and a tertiary amine like triethylamine are mentioned. It can also serve with the excessive amount of a compound. Reaction temperature is usually abbreviation, although it changes with the class of raw material compound, reaction conditions, etc. It is 40 - about 200 **, and is about 100 ** - about 170 ** preferably.
[0078] When R31 in a product and/or R51 have a protective group, hydrogenolysis and/or hydrolysis can perform deprotection.
[0079] It is carried out by being able to perform this hydrogenolysis according to a conventional method, for example, making it react with hydrogen under existence of the catalyst of palladium carbon, a Raney nickel catalyst, etc. in a suitable solvent. As a solvent, alcohols like ethanol and a methanol, water, an acetic acid, dioxane, and a tetrahydrofuran are used, for example. Reaction temperature is usually about 0 degree C - about 80 degrees C, and is performed to the bottom of ordinary pressure or pressurization.
[0080] It is carried out by being able to perform this hydrolysis according to a conventional method, for example, contacting water under acidity or a basic condition in a suitable solvent. As a solvent, alcohols like a methanol, ethanol, and isopropanol, dioxane, water, or such mixtures are used, for example. As an example of an acid, a hydrochloric acid, a mineral acid like a sulfuric acid, a formic acid, an acetic acid, a propionic acid, and an organic acid like oxalic acid are mentioned. Carbonic acid alkali like hydroxylation alkali like a sodium hydroxide and a potassium hydroxide, a sodium carbonate, and potassium carbonate as an example of a base is mentioned. Reaction temperature is usually about 20degree-C-100 **.
[0081] A raw material compound (II) is for example, the following type (IV).
[0082]
[Formula 19]



(IV)

[0083] (-- among a formula, Y means an oxygen atom or a sulfur atom, and R51, R6, R7, and R8 mean the same thing as the above-shown.) -- the compound expressed can be manufactured halogenation or by sulfonyl-izing according to a conventional method.
[0084] Halogenation is performed by making the compound and halogenating agent (for

example, phosphorus oxychloride, phosphorus tribromide) of a formula (IV) react. Sulfonyl-ization is performed by making the compound and sulfonyl-ized agent (for example, methane sulfonyl chloride, p-tosyl chloride, trifluoromethane sulfonyl chloride, a trifluoro methansulfonic acid anhydride) whose Y is an oxygen atom react in a formula (IV).

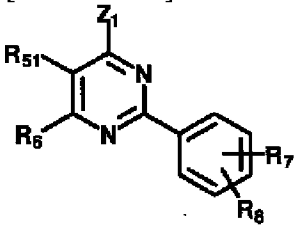
[0085] or [that starting material (IV) is marketed] -- or the very thing -- a well-known approach, for example, J.Am.Chem.Soc., 74, and 842 (1952) -- Chem.Ber., 95, 937 and (1962) J.Org.Chem., 29, and 2887 (1964) It can manufacture by the approach according to an approach given in a list at example 1, 20, and 41 of the after-mentioned reference (1) - (3), or these.

[0086] the compound of the formula (III) which is another [in this process] raw material compound -- the very thing -- it can manufacture by the approach according to a well-known approach, for example, an approach given in the examples 45, 59, and 70 of the after-mentioned reference at a JP,2-32058,A list, or these.

[0087] In a process (b) type (I), X is -O-, and it is R3. The compound which is a hydrogen atom is the following formula (II').

[0088]

[Formula 20]

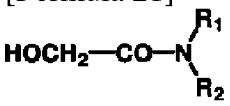


(II')

[0089] (-- among a formula, Z1 means a halogen atom and R51, R6, R7, and R8 mean the same thing as the above-shown.) -- the compound and the following formula (V) which are expressed

[0090]

[Formula 21]



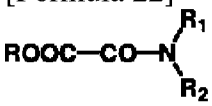
(V)

[0091] (-- R1 and R2 mean the same thing as the above-shown among a formula.) -- the compound expressed can be made to be able to react and it can manufacture by desorbing the protective group of a product if needed.

[0092] The reaction of the compound of a formula (II') and the compound of a formula (V) can be performed to the bottom of ordinary pressure or pressurization under existence of a base and a non-solvent or in a suitable solvent. As a solvent to be used, toluene, a xylene, dimethoxyethane, 1,2-dichloroethane, an acetone, a methyl ethyl ketone, dioxane, a jig lime, ethyl acetate, dimethylformamide, and dimethyl sulfoxide are mentioned, for example. As a base, sodium hydride, triethylamine, potassium carbonate, and a sodium carbonate are mentioned. Reaction temperature is [about] usually. -It is 10 degrees C - about 150 **, and is about 10 degrees C - about 70 degrees C preferably.

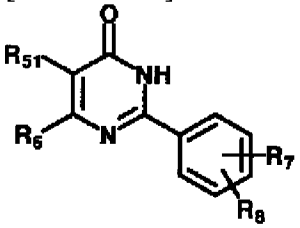
[0093] When R51 in a product has a protective group, hydrogenolysis or hydrolysis can perform deprotection like the case of a process (a).

[0094] A raw material compound (V) is for example, the following type (VI).
[0095]
[Formula 22]



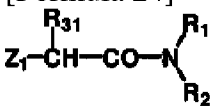
(VI)

[0096] (-- among a formula, R means a low-grade alkyl group and R1 and R2 mean the same thing as the above-shown.) -- the compound expressed can be manufactured by returning according to a conventional method.
[0097] Reduction of the compound of a formula (VI) uses a reducing agent like a lithium borohydride among alcohols like a methanol and ethanol, ether like a tetrahydrofuran, or those mixtures, and is [about]. -It is carried out at 5 degrees C - about 0 degree C.
[0098] starting material (VI) -- the very thing -- it can manufacture by the approach according to a well-known approach and an approach given in the example 81 of the after-mentioned reference (1), or these.
[0099] The compound whose X is -O- in a process (c) type (I) is the following formula (IVa) [0100].
[Formula 23]



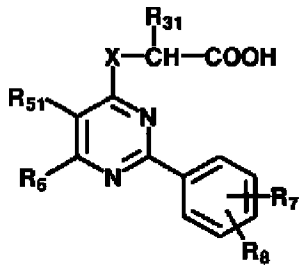
(IVa)

[0101] (-- R51, R6, R7, and R8 mean the same thing as the above-shown among a formula.) -- the compound and the following formula [0102] (VII) which are expressed
[Formula 24]



(VII)

[0103] (-- Z1, R1, R2, and R31 mean the same thing as the above-shown among a formula.) -- the compound expressed can be made to be able to react and it can manufacture by desorbing the protective group of a product if needed.
[0104] The solvent stated by said process (b), a base, reaction temperature, etc. can be used for the reaction of the compound of a formula (IVa), and the compound of a formula (VII) as it is.
[0105] When R31 in a product and/or R51 have a protective group, hydrogenolysis and/or hydrolysis can perform deprotection like the case of a process (a).
[0106] the compound of a formula (VII) -- the very thing -- it can manufacture by the approach according to a well-known approach, for example, an approach given in the example 83 of the after-mentioned reference at a JP,62-64,A list, or these.
[0107] A process (d)-type (I) compound is the following formula (VIII) [0108].
[Formula 25]

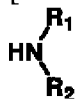


(VIII)

(-- X, R31, R51, R6, R7, and R8 mean the same thing as the above-shown among a formula.) -- the compound expressed or its reaction derivative, and the following formula (IX)

[0109]

[Formula 26]



(IX)

[0110] (-- R1 and R2 mean the same thing as the above-shown among a formula.) -- the compound expressed can be made to be able to react and it can manufacture by desorbing the protective group of a product if needed.

[0111] As a reactant derivative of the compound of a formula (VIII), low-grade alkyl ester (especially methyl ester), activity ester, an acid anhydride, and acid halide (especially acid chloride) can be mentioned, for example. As an example of activity ester, p-nitrophenyl ester, 2 and 4, 5-TORIKURORO phenyl ester, and N-hydroxysuccinimide ester are mentioned. As an acid anhydride, a symmetry acid anhydride or a mixed acid anhydride is used, and a mixed acid anhydride with a mixed acid anhydride with Krol ethyl carbonate and Krol alkyl carbonate ester like Krol carbonic acid isobutyl, a mixed acid anhydride with Krol carbonic acid aralkyl ester like Krol carbonic acid benzyl, a mixed acid anhydride with Krol carbonic acid aryl ester like Krol carbonic acid phenyl, an isovaleric acid, and an alkane acid like pivalate is mentioned as an example of a mixed acid anhydride. When using the compound of a formula (VIII) itself, it can be made to react to the bottom of existence of N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, N, and N'-carbonyldiimidazole, N, and N'-carbonyl disuccinic acid imide, 1-ethoxycarbonyl-2-ethoxy -1, a 2-dihydroquinoline, diphenyl phosphoryl azide, a propane phosphonic acid anhydride, and a condensing agent like benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate.

[0112] The compound of a formula (VIII), or its reactant derivative and formula (IX) The reaction with a compound is performed to the bottom of a non-solvent in a solvent. Although the solvent to be used should be suitably chosen according to the class of raw material compound etc., alcohols like benzene, toluene, the aromatic hydrocarbon like a xylene, diethylether, a tetrahydrofuran, ether like dioxane, a methylene chloride, the halogenated hydrocarbon like chloroform, ethanol, and isopropanol, ethyl acetate, an acetone, an acetonitrile, dimethylformamide, dimethyl sulfoxide, ethylene glycol, water, etc. are mentioned, for example, these solvents are independent, respectively, or two or more sorts are mixed and they are used. It is a formula (IX), although this reaction is performed to the bottom of existence of a base if needed and an organic base like

carbonic acid hydrogen alkali like carbonic acid alkali like hydroxylation alkali like a sodium hydroxide and a potassium hydroxide, a sodium carbonate, and potassium carbonate as an example of a base, a sodium hydrogencarbonate, and a potassium hydrogencarbonate or triethylamine, tributylamine, diisopropyl ethylamine, and N-methyl morpholine is mentioned. It can also serve with the excessive amount of a compound. although reaction temperature changes with classes of raw material compound to be used etc. -- usually -- about -30 degrees C - about 200 ** -- desirable -- about -- they are -10 degrees C - about 150 **.

[0113] When R31 in a product and/or R51 have a protective group, hydrogenolysis and/or hydrolysis can perform deprotection like the case of a process (a).

[0114] In a formula (VIII), the compound whose X is an oxygen atom can be manufactured, for example by said process (c). Namely, the compound of said formula (IVa) and the following type (X)

[0115]

[Formula 27]

(X)

[0116] (-- Z1, and R and R31 mean the same thing as the above-shown among a formula.) -- after making the compound expressed react by the approach stated by the process (c), a product can be manufactured by hydrolyzing according to a conventional method.

[0117] or the compound of a formula (X) is marketed -- or the very thing -- it can manufacture by the well-known approach.

[0118] Formula (VIII) The compound to set and by which X is expressed with -NR4- can be manufactured, for example by said process (a). Namely, the compound of said formula (II) and following type (XI) [0119]

[Formula 28]

(XI)

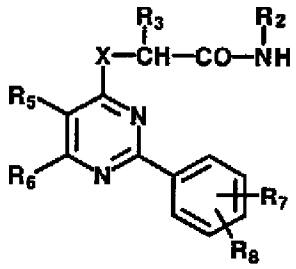
[0120] (Among a formula, R' means the benzyl permuted by one piece chosen from a low-grade alkyl group, benzyl or a halogen, methyl, and methoxy, and R31 and R4 mean the same thing as the above-shown.)

[0121] After coming out and making the compound expressed react by the approach stated by the process (a), a product can be manufactured by hydrolyzing or hydrogenolyzing according to a conventional method.

[0122] formula (XI) or the compound is marketed -- or the very thing -- it can manufacture by the well-known approach.

[0123] Process (e) R1 The compound of the formula (I) which is a low-grade alkyl group and low-grade alkenyl radical or a cycloalkyl (low-grade) alkyl group is the following type (XII) [0124].

[Formula 29]



(XII)

[0125] (-- X, R2, R3, R5, R6, R7, and R8 mean the same thing as the above-shown among a formula.) -- the compound and the following formula (XIII) which are expressed
[0126]
[Formula 30] R11-Z1 (XIII)
[0127] (Among a formula, R11 means a low-grade alkyl group and low-grade alkenyl radical or a cycloalkyl (low-grade) alkyl group, and means what has Z1 [the same as the above-shown].)
[0128] It can come out, the compound expressed can be made to be able to react, and it can manufacture by desorbing the protective group of a product if needed.
[0129] The reaction with the compound of a formula (XII) and a formula (XIII) is usually performed in a suitable solvent. As an example of a solvent, benzene, the aromatic hydrocarbon like a xylene, the ketones like a methyl ethyl ketone, ether like dioxane, and dimethylformamide are mentioned. It is desirable to perform this reaction to the bottom of existence of a base, and the base and sodium hydride which were indicated to the process (a) as an example of a base are mentioned. Although it changes with the class of raw material compound, reaction conditions, etc., it is usually about 0 degree C - about 200 degrees C, and when using sodium hydride for a base, about 0 degree C - about 50 degrees C are preferably desirable [reaction temperature].
[0130] R3 in a product And/or, R5 When it has a protective group, hydrogenolysis and/or hydrolysis can perform deprotection.
[0131] It sets to said process (d) and the compound of a formula (XII) is a formula (VIII). A compound and R1 Formula which is a hydrogen atom (IX) It can manufacture by using a compound.
[0132] formula (XIII) or the compound is marketed -- or the very thing -- it can manufacture by the well-known approach.
[0133] Said process (a) When carrying out - (e) and the radical which participates in a reaction exists in a raw material compound, it is convenient to make it react in the form which protects this radical beforehand or can be easily changed into this radical after reaction termination. For example, some compounds of a formula (I) can be manufactured also by the approach shown below.
[0134] It sets at a ceremony (I) and is R5. It sets at a ceremony (I) and the compound which is an amino group is R5. It can manufacture by returning the compound which is a nitro group with a conventional method, and this approach is concretely shown in the below-mentioned examples 122 and 124.
[0135] It sets at a ceremony (I) and is R5. It sets at a ceremony (I) and the compound which is the acylamino radical is R5. It can manufacture by making the carboxylic acid corresponding to the compound which is an amino group, or its reactant derivative react, and this approach is concretely shown in the below-mentioned example 125.

[0136] It sets at a ceremony (I) and is R5. It sets at a ceremony (I) and the compound which is a hydroxy (low-grade) alkyl group is R5. It can manufacture by returning the compound which is an alkoxy carbonyl group or an alkoxy carbonyl (low-grade) alkyl group with few one carbon atomic number of an alkyl part with a conventional method, and this approach is concretely shown in the below-mentioned example 127.
[0137] It sets at a ceremony (I) and is R8. The compound which is a hydroxy group can be manufactured by processing the compound whose R8 is a methoxy group with a hydrogen bromide in a formula (I).
[0138] The product obtained by said each process can be isolated and refined with conventional methods, such as a chromatography, recrystallization, and reprecipitation. The compound of the formula in the case of having sufficient basicity forming an acid addition salt (I) can be led to an acid addition salt by processing with various kinds of acids according to a conventional method.
[0139] According to conventional methods, such as a chromatography, separation and purification of the various stereoisomers of the compound of a formula (I) can be done.

[Translation done.]

OPERATION

(Antianxiety effect) -- The existence of the antianxiety effect of a trial compound was examined based on ** and the black box examining method of Crawley, J, Goodwin and F.K. and others [Pharmacol.Biochem.Behav., 13, and 167-170 reference (1980)].
[0150] This ** and black box examining method are effective and simple approaches, in order for rodents, such as a mouse and a rat, to use the habit which likes a dark location, to make the increment in the relative residence time in the bright location which is an unpleasant environment the index of electropositive effectiveness and to investigate the antianxiety effect of a drug in behavioral pharmacology. With this approach, it is cholecystokinin. - Many of antagonists of B mold and drugs of a benzodiazepine system show electropositive effectiveness. The camera lucida made from a transparence acrylic board (20x17x15 cm) compared with the illuminance of 1700 luxs with the incandescent lamp and the black box (15x17x15cm) shaded by the product made from a black acrylic board connected the **** black box trial, and it was performed using the equipment (35x17x15 cm) which established the gateway (4.4 x5.0 cm) which a mouse can move to the boundary freely.
[0151] In a trial, it is Std-ddY of weights 25-30g. The system male mouse was used one groups [ten]. The mouse was placed in the center of the camera lucida after [of a trial compound] internal use 30 minutes, the time amount which had stopped at the camera lucida of the trial term throughout for 5 minutes was measured, and the rate of camera-lucida stagnation to all trial term periods was computed. It asked for the relative stagnation rate of increase of a trial compound to a solvent control group based on the rate of camera-lucida stagnation.
[0152] the antianxiety effect effect of a trial compound -- the relative stagnation rate of

increase -- statistical -- being significant (William-WIRUKOKKUSON law, 5% level of significance) -- it expressed with the minimal effective dose (MED) accepted. A result is shown in Table 10.
[0153]
[Table 10]

試験化合物	抗不安作用 最小有効量（mg/kg）	試験化合物	抗不安作用 最小有効量（mg/kg）
1*	0．3	35	0．1
2	0．01	36	0．3
6	0．3	37	0．1
9	0．3	42	＜0．01
10	1．0	45	0．1
16	0．1	52	0．1
21	0．1	136	0．3
22	0．3	139	0．1
23	0．01	150	0．3
29	0．03	202	0．01
31	0．3		

* The compound of an example 1 is meant (the compound of an example is meant similarly hereafter).
[0154] The compound shown in Table 10 shows an antianxiety effect with the dose below 1 mg/kg, and many compounds of them are 0.3 mg/kg. The following doses showed the antianxiety effect.
[0155] The example 3 of a trial: The operation trial to an isoniazid induction clonic spasm

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[Translation done.]

EXAMPLE

[Example] Although the test result of a typical compound is shown in the compound of a formula (I) below and the description of the pharmacological action of the compound concerning this invention is explained to it, this invention is not limited to these examples of a trial.
[0141] The example 1 of a trial: A central mold (omega 1 and omega 2) and peripheral mold (omega 3) benzodiazepine acceptor joint trial -- BZomega1 And omega 2 Preparation of an acceptor joint trial and an acceptor film preparation Stephens and D.N. It is based on an approach [J.Pharmacol.Exp.Ther., 253, and 334-343 reference (1990)].

** -- BZomega3 Preparation of an acceptor joint trial and an acceptor film preparation is Schoemaker and H. It carried out based on the approach [J.Pharmacol.Exp.Ther., 225, and 61-69 reference (1983)]. omega 1 and omega 2 And omega 3 The acceptor film preparation was prepared by the following actuation, respectively from the cerebellum (omega 1), the spine (omega 2), or the kidney (omega 3) of the Wister system male rat of seven to 8 weeks old.

[0142] After adding and homogenizing the buffer solution (50 mM tris-citrate buffer solution, pH7.1) which ** ice-cooled 20 times for a cerebellum or a spine, the at-long-intervals alignment was carried out by 40,000 g for 15 minutes. Cryopreservation of the obtained dregs was carried out at -60 degrees C after 4 times washing by same actuation for 24 hours. It is BZomega1 about what suspended the dregs obtained by carrying out washing and centrifugal with the buffer solution after dissolving freezing dregs in the buffer solution I for a joint trial (50mM(s) containing a 120 mM sodium chloride, 5mM potassium chloride, 2mM calcium chloride, and 1mM magnesium chloride the tris-hydrochloric-acid buffer solution, pH 7.4) (1g organization wet weight / 40 ml). Or omega 2 It considered as the acceptor film preparation and used for the joint trial. On the other hand, after adding and homogenizing into the kidney the buffer solution II (the 50 mM sodium phosphate-potassium phosphate buffer solution, pH7.4 containing a 100 mM sodium chloride) for a joint trial which ** ice-cooled 20 times, the at-long-intervals alignment of the filtrate filtered with the gauze put on four-fold was carried out by 40,000 g for 20 minutes. It is suspension (1g organization wet weight / 100 ml) to the buffer solution II about the obtained dregs. It is BZomega3 about what was carried out. It considered as the acceptor film preparation and used for the joint trial.

[0143] As indicator ligand and non-indicator ligand, it is BZomega1. And omega 2 For an acceptor joint trial, [3H] flumazenil (Ro 15-1788) [the last concentration (omega1 : 0.3 nM) (omega2:1nM)] and flunitrazepam (last concentration 10microM) BZomega3 In an acceptor joint trial, it is [3H]. Ro 5-4864 (4'-chloro diazepam: 7-chloro -1, 3-dihydro-1-methyl-5-(4-chlorophenyl)-2H-1, 4-benzodiazepine-2-ON) (last concentration 0.5 nM) and diazepam (last concentration 100 muM) were used, respectively. Incubation conditions are BZomega1. And omega 2 By acceptor joint trial, they are for 30 minutes and BZomega3 at 37 degrees C. By acceptor joint trial, it is 150 at 0 degree C. It carried out between parts. In addition, BZomega1 And omega 2 The acceptor joint trial was performed to the bottom of BIKYU curine (bicuculline: last concentration 100 muM) existence.

[0144] The following operating procedure performed the acceptor joint trial. The trial compound of concentration known, tritium-labeling ligand, an acceptor film preparation and the buffer solution I for a joint trial, or II was added to each test tube, it considered as reaction mixture with a total amount of 1ml, and the reaction was started by addition of an acceptor film preparation. The reaction was suspended after the incubation by carrying out suction filtration of the indicator ligand combined with the acceptor on the Watt Mann GF/B glass fiber filter using a cell harvester (made in Blandel, U.S.). Immediately, ice-cooled buffer-solution [omega1 and omega 2 washed 3 times by buffer-solution II]5ml by 50 mM tris-hydrochloric-acid buffer-solution (pH 7.7); omega3. Radioactivity moves a filter to a vial and is liquid scintillation cocktail (ACS-II, Amersham make, U.S.) 10 ml. In addition, after carrying out fixed time amount installation, it measured with the scintillation counter. The amount of specific bindings was calculated by deducting the

amount of nonspecific association under the non-indicator ligand existence measured to coincidence from the total amount of association. In addition, it asked for the concentration (IC50 value) to which a trial compound controls the amount of specific bindings of indicator ligand 50% with the probit method. Benzodiazepine omega 3 The result of an acceptor binding action is shown in Tables 7-9. In addition, the compound shown in Tables 7-9 is the benzodiazepine omega 1. And omega 2 All of IC50 value of the binding action to an acceptor are 1000 nM. It was above.

[0145]

[Table 7]

試験化合物	ω_3 IC_{50} (nM)	試験化合物	ω_3 IC_{50} (nM)
1*	3.10	26	0.28
2	0.97	27	0.11
4	4.36	29	0.85
5	1.28	35	1.51
6	0.23	36	1.44
10	0.70	37	1.66
15	3.86	41	2.53
16	4.00	42	2.15
17	1.97	44	4.98
22	3.26	45	0.70
23	1.76	47	0.16
25	1.93	49	0.23

* The compound of an example 1 is meant (the compound of an example is meant similarly hereafter).

[0146]

[Table 8]

表７の続き

試　験 化合物	ω_3 IC_{50}（nM）	試　験 化合物	ω_3 IC_{50}（nM）
５１	０．３２	１０６	４．２４
５２	２９．５	１０７	４．２３
５７	５．３９	１０８	１．２１
５８	１．６２	１０９	２．０９
６１	９．８０	１１０	１．９９
６５	１．６６	１１１	２．０５
６８	２．１９	１１２	２．３４
６９	２．７５	１１８	１．０７
７０	１．１２	１１９	１．４５
７６	１．３３	１２０	１．６３
７９	０．８７	１２４	５．３５
８１	６．９０	１２７	４．３５
８３	５．０２	１２８	０．７９
８４	２．０４	１３０	１．３１
８５	０．１８	１３１	０．８９
９３	４．１０	１３３	２．２０
９７	２．２７	１３４	３．０７
１０２	３．３１	１３５	３．１７
１０３	２．９０	１３６	０．３４
１０４	３．４４	１３７	０．９３
１０５	４．１８	１３８	０．５３

[0147]
[Table 9]

表７の続き

試験化合物	ω_3 IC_{50}（nM）	試験化合物	ω_3 IC_{50}（nM）
１３９	０．３８	１６８	０．９９
１４１	０．１１	１６９	１．１５
１４２	０．０８	１７０	０．９９
１４３	１．４０	１７１	１．５６
１４４	０．３１	１７５	１．９０
１４５	１．６０	１７８	０．５７
１４７	０．５２	１７９	４．３０
１４９	１．１４	１８０	１．６５
１５１	０．５８	１８１	１．６１
１５５	０．７６	１８２	４．５７
１５６	４．９６	１８３	８．７５
１５８	４．０７	１８４	０．８２
１５９	２．００	１８６	２．３９
１６０	４．３０	１８７	９．７１
１６１	１．０５	１８８	５．２４
１６２	１．１９	１９０	４．００
１６３	２．６４	１９５	２．００
１６４	０．２９	２０２	５．３０
１６５	５．０７	２０７	７．２
１６６	５．４０	２０９	２．２
１６７	０．７９		

[0148] The compound shown in Tables 7-9 is BZomega3. In spite of combining with an acceptor powerfully, it is BZomega1 of these compounds. And BZomega2 IC50 value of an acceptor is 1000 nM. The compound concerning this invention since it is above is BZomega3 powerfully alternatively. Combining with an acceptor is clear.
[0149] The example 2 of a trial: ** and a black box trial

[Translation done.]